

## 9

## Pancreatico-duodenal Transplantation with Enteric Exocrine Drainage

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### Introduction

Pancreas transplantation was first attempted in humans by Kelly *et al.* (1967) and Lillehei *et al.* (1967). The whole organ was grafted along with variable segments of duodenum and jejunum. The results were poor, and by 1972 the whole organ concept was virtually abandoned for the next decade. Even at the University of Minnesota where Lillehei worked, only one whole pancreas was transplanted between 1970 and 1981 (Sutherland *et al.*, 1984). Almost all groups had switched their preference to segmental grafting.

In early 1982, we re-examined the reasons for abandonment of whole pancreas transplantation, and undertook reassessment of the procedure in dogs (Diliz-Perez *et al.* 1984). Our conclusion was that the most logical operation had been discontinued in favour of the inferior option of segmental pancreas transplantation. Consequently, a limited clinical trial of whole organ pancreas transplantation was begun in March, 1983. Although the number of cases was small, and has remained so, the influence of the trials was magnified by three circumstances.

First, the cases were presented informally in a lively but unpublished discussion between knowledgeable colleagues at the first International Symposium on Cyclosporine in Houston, Texas, in May 1983. Second, fellows or visitors at our University of Pittsburgh Transplant Center had an opportunity to see personally how easy, and in a number of cases, how successful, the whole organ procedure actually was. One such fellow (1981–3), Dr Munci Kalayoglu, subsequently joined a team at the University of Wisconsin headed by Dr Hans Sollinger which had previously compiled an encouraging series of segmental transplantations with exocrine drainage into the bladder. After Kalayoglu's arrival, Sollinger and Kalayoglu changed the emphasis from segmental to whole organ transplantation (Sollinger *et al.*, 1985). Similarly, Dr Robert Corry of

the University of Iowa was persuaded during a sabbatical leave in Pittsburgh in late 1983 and early 1984 to adopt the whole pancreas transplantation procedure (Corry *et al.*, 1986). Thus, the comments in this chapter about techniques, complications, and results will draw from the experience not only in Pittsburgh but also from that at the University of Wisconsin and the University of Iowa.

Third, the careful study of our small number of recipients has permitted some definitive conclusions about the management of both the intestinal and the splenic components of the specimen which are removed along with the pancreas from the cadaver donor (Starzl *et al.*, 1984a, 1986).

### Anatomical considerations

The logic of removing the entire pancreas as part of a composite organ graft is evident from the most casual inspection of the upper abdominal viscera both in human beings and animals (Fig. 9.1). The duodenum and spleen share the

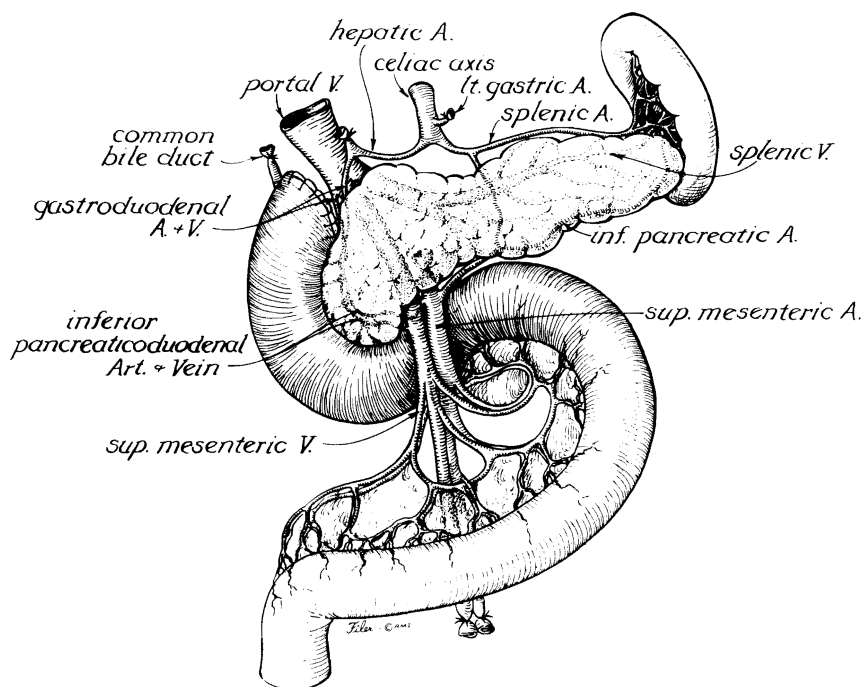


Fig. 9.1. Composite graft removed from donors in preparation for whole pancreatic transplantation. The spleen, jejunum, and part of the duodenum are removed at the back table. By permission of Starzl *et al.* (1984b).

blood supply of the pancreas to which they are intimately adherent, and in addition, the duodenum receives the exocrine pancreatic secretions. Thus, it was not surprising that pancreatico-duodenal grafts were used in the acute experiments performed upon animals reported long ago (Houssay, 1929) and many years later (DeJode and Howard, 1962).

Similarly, most of the grafts transplanted under immunosuppression in the pioneering work done by Lillehei and co-workers in dogs (Lillehei *et al.*, 1967; Idezuki *et al.*, 1968) and eventually in humans (Kelly *et al.*, 1967; Lillehei *et al.*, 1967, 1970) consisted of all of the pancreas, the duodenum and frequently a short section of jejunum. Poor results both in animals and humans after such procedures caused their abandonment in favour of the suboptimal partial pancreatic grafts from which the disposition of exocrine secretions have posed special technical problems (Land and Landgraf, 1983; Sutherland *et al.*, 1984; Tydén and Groth, 1986).

Aside from providing a larger supply of islets, the advantages of the whole pancreas are principally technical. A larger volume of blood flow through the graft is assured. Large calibre vascular anastomoses are used. Finally, exocrine pancreatic secretions can be directed into the intestinal or urinary tract through a small duodenal patch or bubble.

### Principles of donor operation

Total pancreatectomy is part of a multiple organ procurement procedure (Starzl *et al.*, 1984a) that has become accepted as a world-wide standard. If the pancreas is to be removed, an *in situ* infusion of cold preservation fluid is begun after the aorta is cross-clamped just below the diaphragm, using the distal aorta as the entry site (Fig. 9.2, upper). From a practical point of view, all donors are also renal donors. It is most efficient to have a single surgeon remove both kidneys and the pancreas, rather than to attempt to have two teams working. We use lactated Ringer's solution for cooling in preference to the potassium and magnesium-rich Collins-type solutions. However, either kind of infusate can cause oedema and pancreatitis (McDonald *et al.*, 1986). At the end of the cooling and harvesting period, other techniques of preservation can be applied secondarily as will be discussed in Chapter 6. However, our preference if the transplantation can be done within 6 h is to do nothing more than initial cold infusion.

The principle just described can be applied with a number of variations. We prefer to do a meticulous preliminary dissection only of the portal triad structures. The common duct and hepatic arteries passing to the liver are ligated and divided and the portal vein is skeletonized out to its bifurcation in the liver hilum. After this preparation, the distal aortic infusion is begun with the cold lactated Ringer's solution. All of the rest of the dissection is carried out in a

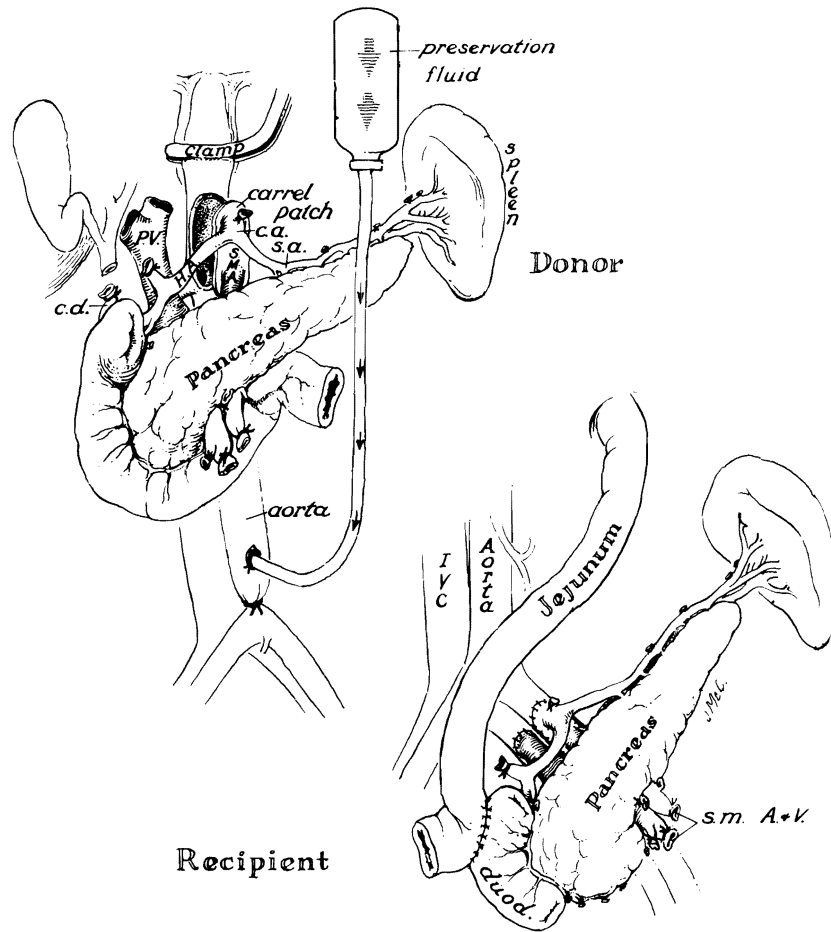


Fig. 9.2. *Upper: Principle of core cooling of whole pancreas through the aorta. Note that both the coeliac axis and superior mesenteric artery are revascularized by means of a Carrel patch. Lower: Implantation into recipient common iliac vessels. The spleen is removed. The side-to-side duodeno-jejunosomy is probably a suboptimal way of draining exocrine secretions (see text).*

bloodless field. Alternatively, the pancreas can be completely mobilized and the structures at the base of the small bowel mesentery can be individually ligated and divided with the circulation intact. However, this may require 1 or 2 h instead of the 10 or 15 min which is all that is needed in a bloodless field.

We advocate making from the abdominal aorta a Carrel patch which encompasses the origin of the coeliac axis as well as the superior mesenteric artery (Fig. 9.2, upper). Better vascularization of the pancreas graft is thereby assured, and the natural superior to inferior pancreatico-duodenal arterial anastomoses are vascularized from both directions.

### The recipient operations

Almost all total pancreas transplantations have been to the iliac vessels of the recipient, but the level has been variable. For relatively small pancreas grafts, it is feasible to anastomose the portal vein of the graft to the external iliac vein and the Carrel patch to the external iliac artery. With larger specimens, it has been necessary to use the common iliac artery and vein for recipient vascular sites (Fig. 9.2, lower).

For ease of orientation, the recipient's left side is preferred for transplantation. On this side, the pancreas can be placed in a natural orientation with its tail passing to the left (Fig. 9.2, lower). However, the left extraperitoneal space or iliac vessels often have been used up for renal homografts since many of the pancreas recipients also are victims of diabetic nephropathy. Under such

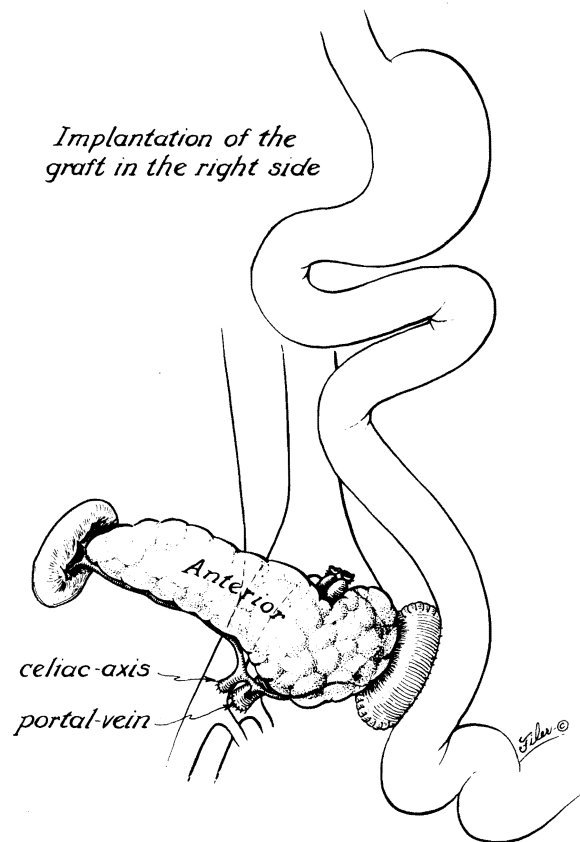


Fig. 9.3. Anastomoses of vessels into right iliac artery and vein with rotation of the pancreas  $180^\circ$  from its natural leftward orientation. By permission of Starzl et al. (1984b).

circumstances, the pancreas is rotated 180°, attached to the right iliac vessels, and oriented as shown in Fig. 9.3.

Whether it is acceptable to drain a pancreas graft into the systemic venous circulation instead of into the splanchnic venous bed remains an open question. It has been well established for 25 years that glucose homeostasis occurs principally in the liver (Madison *et al.*, 1960; Starzl *et al.*, 1965), making it seem almost illogical to deliver insulin elsewhere than into the portal system. Furthermore, it has been established beyond doubt that the liver itself benefits from the portal route of insulin delivery since the insulin has been shown unequivocally to be the principal hepatotrophic factor in normal splanchnic venous blood (Starzl *et al.*, 1983). Tydén *et al.* (1984) and Calne and Brons (1985) have described transplanting segmental pancreases to the splenic vein or other splanchnic venous tributaries but there has been no convincing evidence to the present time of a clinically significant advantage. If it is important to deliver insulin into the splanchnic venous circulation, the evidence for this is going to be extremely subtle and it will be convincing only with very long-term observations.

### Disposition of the duodenum and jejunum

In Lillehei's first clinical trials of whole pancreas transplantation, the duodenal component of the transplant was apparently responsible for a high incidence of infection and other lethal complications, probably because intestinal rejection was difficult to control with the immunosuppressive therapy which was then available (Kelly *et al.*, 1967; Lillehei *et al.*, 1967, 1970). The magnitude of intestinal problems became obvious in some of our first patients. In one (Fig. 9.4a), a 2 foot length of graft jejunum was anastomosed to the recipient jejunum. After a few weeks, the patient had cramps, watery diarrhoea and hypoalbuminaemia. With gastrointestinal tract series and computerized axial tomography, the luminal aspect of the graft jejunum was irregular and thickened. At reoperation, 3 months after the original procedure, the graft jejunum was detached from the recipient intestine and anastomosed to the skin of the abdominal wall (Fig. 9.4c). Although the intestine looked almost normal from the outside, extensive mucosal damage was evident both grossly and microscopically, probably reflecting slow rejection (Starzl *et al.*, 1984,b).

During the 42 days when the skin jejunostomy was in place, its daily output range between 2–3 litres, a volume greater than expected from an otherwise normal pancreas. The protein concentration of the collected luminal content was almost 2 g. A protein losing enteropathy of the 2 or 3 foot duodenojejunal homograft segment was responsible for the loss of 40–60 g of endogenous protein per day and accounted for the hypoalbuminaemia that had occurred.

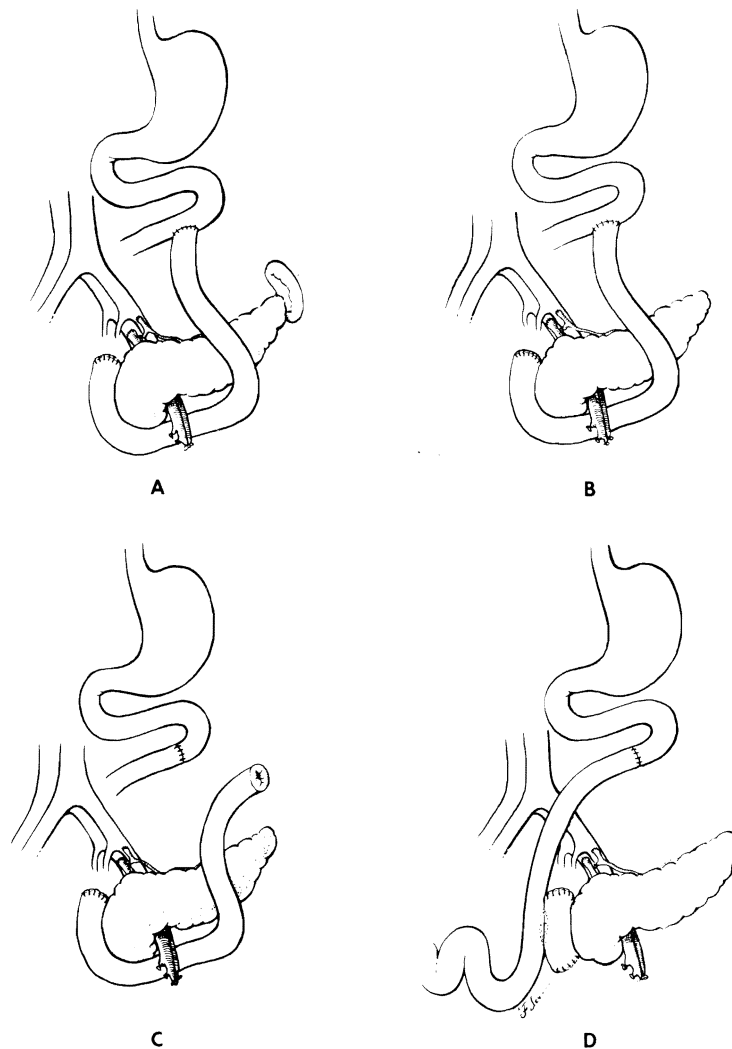


Fig. 9.4. Operative revisions in one of our patients. (a) The entire specimen shown in Fig. 9.1 was transplanted. (b) Splenectomy was performed after 6½ days. (c) The graft jejunum was detached from its anastomosis to recipient jejunum and brought to the skin of the left lower quadrant. (d) The graft jejunum and distal part of the duodenum were resected and a "bubble" of duodenum retained for anastomosis to the recipient jejunum. (See text for details.) By permission of Starzl et al. (1984b).

At a third operation, the jejunum and distal part of the duodenum were removed, leaving a bubble of duodenum which was anastomosed side-to-side with the jejunum of the recipient (Fig. 9.4d). Within a few days, the serum albumin concentration of the recipient rose to normal, and all of the intestinal

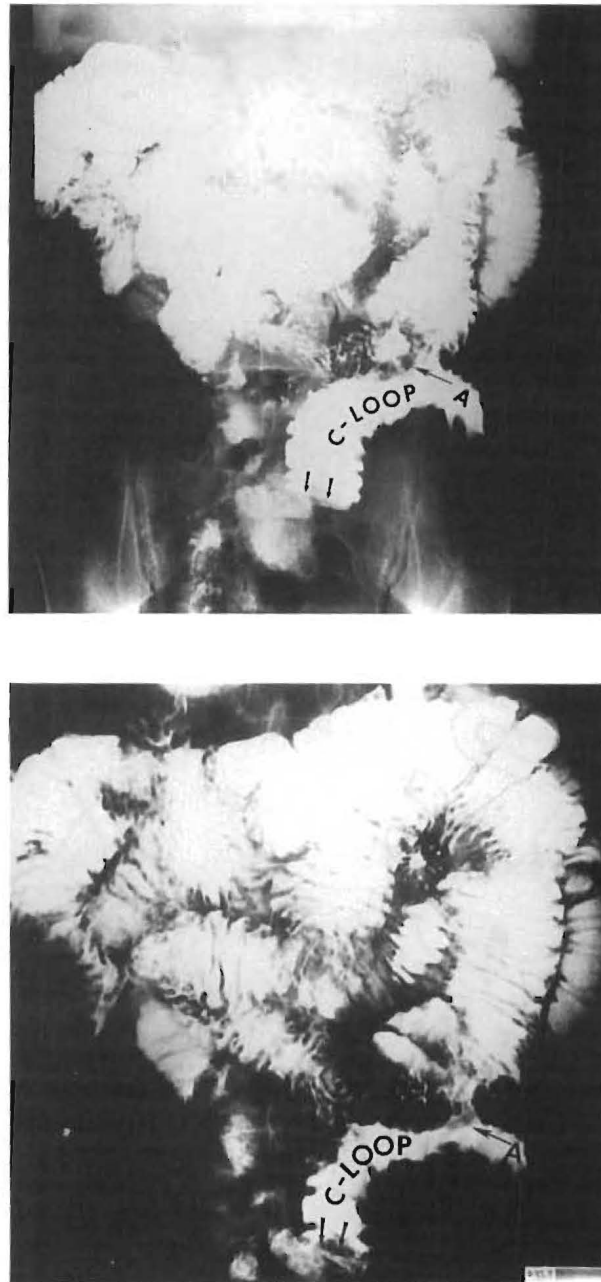


Fig. 9.5. GI series obtained one month after pancreaticoduodenal transplantation. The C-loop of grafted duodenum is shown in the filled (upper) and contracted (lower) state.



symptoms were relived. Further hospitalization has not been necessary. The same syndrome was encountered and similarly corrected in a second patient.

In another patient in whom the intention was to perform the duodenal bubble procedure at the outset, too much of the C-loop of the duodenum was left in place (Fig. 9.5). One month post-operatively, the patient was readmitted with uncontrollable diarrhoea. The C-loop was trimmed back to the small bubble (Fig. 9.4d) and the patient recovered with no further complaints.

An alternative to leaving a duodenal bubble is the duodenal patch technique originally described by Lillehei *et al.* (1970). With this method, only the duodenum immediately surrounding the ampulla of Vater is left with the pancreas, all of the other duodenum and jejunum being removed. The duodenal patch can be anastomosed to the intestine, to the bladder, or elsewhere (see later).

### The question of the spleen

The principal reason to retain the spleen with the graft was the increase in blood flow thereby obtained. In addition, there was a possible subtle immunological advantage for the pancreas of having the additional antigen mass provided by extrapancreatic tissues. The evidence for this hypothesis has been summarized elsewhere (Starzl *et al.*, 1984b) from observations in such diverse species as the dog, rat and guinea pig.

The spleen was transplanted as part of the graft in seven of our first eight cases. Splenectomy was performed in three of these seven recipients at 6.5, 18, and 20 days post-operatively. In a patient with Type A blood who had been given a Type O spleen, the spleen was shown to have produced anti-A isoagglutins in sufficient quantities to cause severe haemolysis of the recipient's red blood cells (Starzl *et al.*, 1984b, 1986). This complication was relieved promptly by splenectomy. The other splenectomies (after 18 and 20 days) were because of thrombocytopenia and leukopenia (one case each). All three patients requiring splenectomy were thought to be examples of graft host disease. In these three patients, graft splenectomy was extremely easy. The lateral end of the wounds were reopened and each splenectomy was performed within a few minutes with virtually no blood loss. Recovery was prompt.

Four patients still have their grafted spleens in place after 2.5, 4.5, and 19 months.

In addition to our complications just cited, Deierhoi *et al.* (1986) and Gonwa *et al.* (1985) have both reported severe or lethal graft vs host reactions. Although graft vs host reactions can be prevented in rodents (Shulak and Sharp, 1986) and pigs (DaFoe *et al.*, 1986) by irradiating the graft, the effort and risk no longer seem acceptable, and we have abandoned the practice of leaving the spleen in place.

### The exocrine secretions

It is certain that the disfavour into which Lillehei's original operation fell was due to complications in dealing with exocrine secretions, and particularly complications of the duodenal segment through which these secretions passed. Two options which at first seemed acceptable with the segmental grafts are unacceptable with the whole organ. One is to allow the exocrine secretions to pass into the peritoneal cavity and from there to be absorbed (Sutherland *et al.*, 1984). Severe peritonitis, sometimes necessitating the removal of otherwise successful segmental pancreas grafts has been reported; these complications with a full sized organ would be predictably even more severe.

Exocrine secretions could be controlled by pancreatic duct ligation, by the other unacceptable option of occlusion of the duct system with plastic injections, or by other means. We do not recommend these techniques.

#### *Diversion into the Intestinal Tract*

The duodenal bubble or duodenal mucosal patch can be anastomosed to the side of the gastrointestinal tract (Fig. 9.2 lower), or into a Roux-limb (Fig. 9.6). The Roux-limb principle for draining exocrine excretions was originally recommended by Lillehei *et al.* (1970) and by Groth *et al.* (1976). Even with a Roux-limb, contamination of the graft with intestinal contents

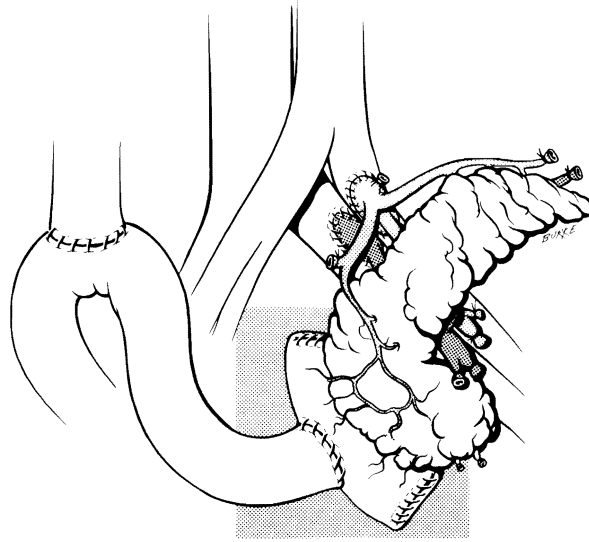


Fig. 9.6. Anastomosis of duodenal bubble to Roux-limb of jejunum.

is inevitable. Such contamination can result in very specific complications including mycotic aneurysm formation at the vascular suture lines (see later).

*Diversion into the Genito-urinary Tract*

The possibility of diverting exocrine secretions into the urinary collecting system was first proposed by Gleidman *et al.* (1973) who anastomosed the pancreatic ducts to the ureter. Sollinger *et al.* (1985) and Corry *et al.* (1986) anastomosed the duodenal bubble of a "pancreas" graft to the anterolateral bladder wall (Fig. 9.7). This technique has been to perform the anastomosis with an external tacking suture, and with a definitive inner layer of continuous catgut or other absorbable suture as is described in Chapter 11. The method is not dissimilar from a standard gastrointestinal anastomosis.

In the University of Wisconsin and University of Iowa series, complications from exocrine secretions have been acceptable with this adjustment in technique. However, Tom *et al.* (1986) have reported digestion of the urethra by activated pancreatic enzymes. Also, mild but uncorrectable metabolic acidosis has been

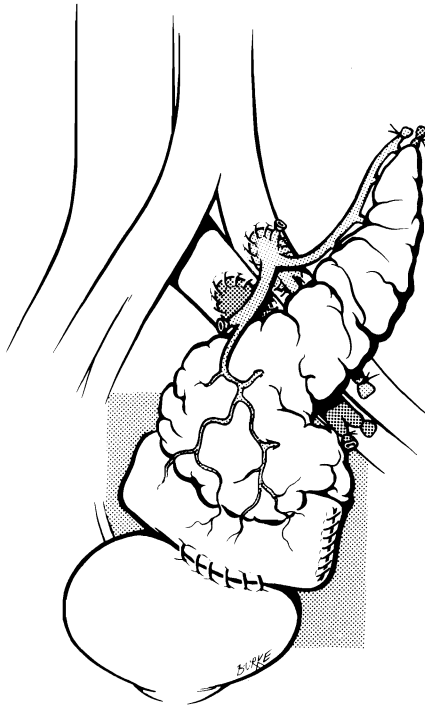


Fig. 9.7. Anastomosis of duodenal bubble to bladder.

caused by the continuous loss of bicarbonate into the genito-urinary system (Nghiem *et al.*, 1986).

### Results

One hundred and three patients have been treated with whole organ pancreas transplantation at the University of Pittsburgh, the University of Wisconsin, and the University of Iowa between March 1983 and July 1986. The smallest number of cases (15 transplants in 14 recipients) was from the University of Pittsburgh (Table 9.1). Of the 50 cases at the University of Wisconsin, the last 29 compiled between April 1985 and July 1986 have been made available to us for analysis (Table 9.1) (Sollinger *et al.*, 1986). All 42 of the Iowa whole pancreas transplantations to 39 recipients have been reported (Corry *et al.*, 1986, Corry, 1987).

The 10 surviving Pittsburgh recipients have been followed for 1–3.3 years. Five of them are insulin-free, one by virtue of a second pancreas which has functioned for one year. The first pancreatic graft in the latter patient functioned well for 13 months before abruptly failing. A graft in another patient failed suddenly after 19 months. A third pancreatic graft was lost after 13 months when the recipient died of a myocardial infarction; at autopsy it was normal.

TABLE 9.1  
*Results with Whole Pancreas Transplantation at Three Centres*

	<i>Pittsburgh</i>	<i>Iowa</i>	<i>Wisconsin</i>
Period of study	March 83– December 85	March 84– May 86	April 85– July 86
No. patients	14	39	29
Mean age (years)	31	31.9	
No. grafts	15	42	29
Previous kidney	7	13	17
Simultaneous kidney	5	29	12
Subsequent kidney	1	0	0
Deaths < 1 year	3	23%* actuarial	Not known*
Deaths > 1 year	1	Not known*	Not known*
One-year pancreas graft survival	8(53.3%) actual	52% actuarial	73% actuarial
Pancreas lost after 1 year	3**	0	Too early to know

\*The majority of the surviving patients have not as yet been followed for as long as a year.

\*\*After 13, 13, and 19 months, one of the losses was from death after a myocardial infarction; the pancreas was normal. Another of the recipients has had a second graft with function for another year.

Thus, an insulin-free state at one year was achieved in 8 (53.3%) of 15 transplantations (Table 9.1).

Two of the four deaths in the Pittsburgh series, one from a myocardial infarction and the other from a stroke precipitated by pre-operative insulin reactions, were caused by a continuation of pre-operative processes. The two other deaths were peri-operative. One recipient of simultaneous kidney and pancreas grafts developed severe rejection of both organs and died of gastrointestinal haemorrhage and cardiac arrest. The other patient died of mediastinitis which started from an unrecognized pharyngeal perforation which occurred during tracheal intubation for anaesthesia at the time of transplantation.

The results have been similar in the Iowa experience (Table 9.1), in that the projected one-year graft survival is 52%. Six deaths have been recorded in the 39 recipients, and five of these have been from myocardial infarction (Corry, 1987). With such deaths, as with three of ours, there has been the spectre of a jinx with pancreas transplantation.

The immunosuppression in the Pittsburgh and Iowa series has been with cyclosporine and prednisone, with or without monoclonal antilymphocyte globulin (OKT3). Sollinger *et al.* (1987) at Wisconsin have used triple therapy with cyclosporine, prednisone, and azathioprine in their last 29 patients (Table 9.1). Their projected one-year graft survival is 73%, and so far they have had only one death. However, 17 of the 29 patients have follow-ups of less than 6 months, and only a few have gone beyond 1 year. Although the follow-ups are too short to permit definitive conclusions, the Wisconsin experience has been the most encouraging so far.

In the Pittsburgh and Iowa series, complications have been seen which are not specific to pancreas transplantation but which have had an unusually high incidence after this operation. Examples are wound infections and graft venous thrombosis (Table 9.2). Four patients of the 57 in these combined series have developed mycotic aneurysms of the iliac artery at the site of Carrel patches (Table 9.2). Ligation of the iliac artery, and femoral-femoral extra anatomic by-passes have saved the patients and their limbs, but only because the arterial blow-outs occurred in the hospital after failed pancreas grafts had been removed from a few days to a year after transplantation.

TABLE 9.2  
*Complications seen with Unusual Frequency After Whole Pancreas Transplantations*

	<i>Pittsburgh</i>	<i>Iowa</i>
Wound infection	4/15	20/42
Venous thrombosis	2/15	9/42
Graft vs host disease	4/15*	3/42*
Mycotic aneurysm iliac artery	3/15	1/42

\*Spleen related (see text).

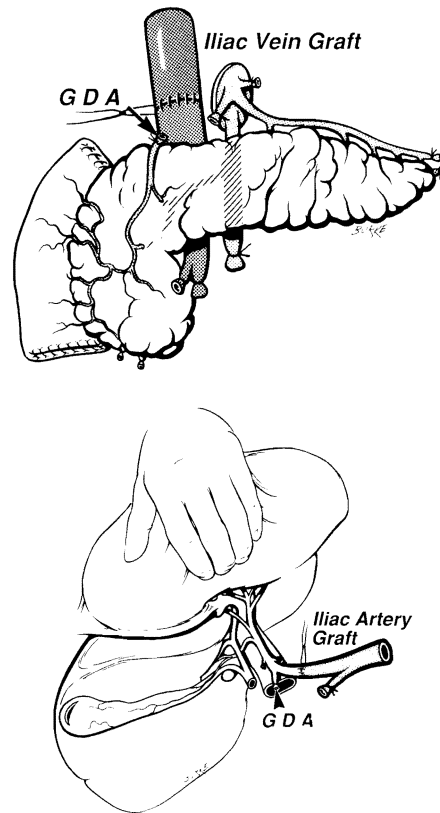


Fig. 9.8. *Upper: Whole pancreas specimen from a pancreas plus liver donor. Note that the short portal vein of the graft has been prolonged with an iliac vein graft from the same donor. Gd: Ligated gastroduodenal artery. Lower: Liver graft from the same donor. Note the extension of the length of the hepatic artery with an iliac artery graft. Gd: The ligated proximal gastroduodenal artery.*

### Pancreas vs liver: an ethical question?

With the techniques used to date, whole organ pancreas transplantation is incompatible with orthotopic transplantation of the liver since both procedures call for retention with the graft of the coeliac axis and portal vein. For most diabetics, transplantation of the pancreas is somewhat of a luxury. The obverse holds for liver recipients who do not have an alternative form of treatment comparable to insulin administration.

As a result of this conflict, we have restricted pancreas transplantation to situations in which the livers cannot be used, either locally or in other centres.

If a donor becomes available the computer system for organ sharing is checked for national needs. In addition, we have always called the other most active liver centres with a specific inquiry about their need.

Until now, the disposition of organs and the resolution of potential conflicts such as that just described have been left to the discretion of the harvesting transplant surgeon and the recipient team. This has been appropriate during the developmental stages of transplantation. The decisions were dictated by the interest of the surgeon without any kind of societal planning.

As soon as liver transplantation became practical, such a basis for decision making became untenable ethically. Furthermore, the scrutiny to which we are being subjected, and this will only increase, is going to make this approach unacceptable to the public.

Improved surgical techniques such as those shown in Fig. 9.8 could ameliorate the situation by allowing use of the liver and whole pancreas. In the example, shown, the liver would retain almost all of its portal vein, and the short portal vein of the pancreas specimen would be lengthened with an iliac vein graft from the donor. The donor coeliac axis, and proximal hepatic artery as well as the superior mesenteric artery would stay with the pancreas. The hepatic artery retained with the liver would be lengthened with a free iliac artery graft (Fig. 9.8). Possible variations from this technique are obvious.

### Conclusion

Once a pancreas transplantation is decided upon, a transplantation of the whole pancreas is based on sounder surgical principles than the alternative of segmental grafting. However, the widespread use of the procedure as it has evolved to date would eliminate the supply of cadaver livers which are even more urgently needed. A possible resolution of the problem in which both pancreas and livers could be used from a common donor is described. Even with whole pancreas transplantation, the risk of the operation and the expectation of an unequivocal success are still suboptimal.

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